IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No.:	10/748,524
Applicant:	Richard E. Parizek *et al.*
Confirmation No.:	8568
Filed:	December 29, 2003
Group Art Unit:	1645
Examiner:	Jana A. Hines
For:	A multicomponent vaccine containing clostridial and non-clostridial organisms in a low dose
Attorney Docket:	1995.184 US D1

July 18, 2008

APPEAL BRIEF

Mail Stop Appeal
Board of Patent Appeals
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir/Madam:

Pursuant to Appellants' April 18, 2008, Notice of Appeal, Appellants appeal all the claim rejections in the December 20, 2007 final Office action directed to the above-referenced patent application. In support of this appeal, Appellants provide the following information, argument, and fee in accordance with 37 C.F.R. §41.37 and MPEP §§1205 and 1205.02.

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I. REAL PARTY IN INTEREST (37 C.F.R. §41.37(c)(1)(i))

The real party in interest in this appeal is Intervet International B.V. This ownership is evidenced by assignment documents recorded at Reel 011339, Frame 0734 (recorded on November 20, 2000), Reel 018238, Frame 0579 (recorded on September 8, 2006) and Reel 018302, Frame 0482 (recorded on September 25, 2006).

II. RELATED APPEALS AND INTERFERENCES (37 C.F.R. §41.37(c)(1)(ii))

Appellant is not aware of any prior or pending appeal, judicial proceeding, or interference that may be related to, directly affect, or be directly affected by or have bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS (37 C.F.R. §41.37(c)(1)(iii))

A total of 48 claims have been introduced in this patent application. Claims 1-45 have been canceled. Thus, claims 46-48 remain pending. Every pending claim is rejected. This appeal requests reversal of all the rejections.

IV. STATUS OF AMENDMENTS (37 C.F.R. §41.37(c)(1)(iv))

Appellants filed an amendment on April 18, 2008, in response to the final Office action. The amendments were entered for the purpose of appeal in an Advisory Action dated May 16, 2008. These amended claims are now on appeal.

V. SUMMARY OF CLAIMED SUBJECT MATTER (37 C.F.R. §41.37(c)(1)(v))

The method of the invention recited in claims 46-48 result from Apellants' discovery that cattle can be effectively immunized against multicomponent clostridial vaccines in combination with a Moraxella Bovis antigen and an encapsulating polymer adjuvant in a dose of about 2 ml, while achieving a reduction in an injection site lesions. There are three independent claims, which are summarized as follows:

A. **Claim 46** is directed to a method for immunizing cattle without significant injection site lesion formation comprising injecting about 2 ml of a multicomponent vaccine comprising a combination of a protective antigen component from 6 clostridial organisms, a protective antigen component from Moraxella Bovis and an encapsulating polymer adjuvant, whereby the encapsulating polymer adjuvant releases antigen slowly at the site of injection and whereby the injection site lesion formation is reduced by at least 41% compared with an injection of 5 ml of the vaccine, and effective immunization is accomplished. See, e.g., Appellants' Specification page 6, lines 1-7; page 8, lines 8-16; page 12, lines 3-9; page 14, lines 13-20; page 15, lines 23-28; and Example 8 beginning on page 52 and including Tables 12 and 13 on page 54.

B. **Claim 47** recites the invention wherein the method comprising administering the same vaccine, but with antigen components from seven clostridial organisms, as well as Moraxella Bovis. See, e.g., in addition to the above, page 6 lines 8-15; page 7, lines 9-14; and Example 5 on page 41.

C. **Claim 48** recites the method comprising administering the same vaccine but with the specific clostridial components *Cl. chauvoei, Cl. septicum, Cl novyi, Cl. perfringens* type C, *Cl. perfringens* type D, *Cl. sordellii, Cl. tetani* and *Cl. haemolyticum.*

See, e.g., Appellants' Specification as noted above.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL (37 C.F.R. §41.37(c)(1)(vi))

Claims 46-48 have been rejected under 35 U.S.C. §103(a) for being obvious over Roberts (WO 94/22476) in view of Lund (U.S. Patent 3,920,811).

Claims 46-48 have been rejected under 35 U.S.C. §112, first paragraph, for not meeting the written description requirement.

VII. ARGUMENT (37 C.F.R. §41.37(c)(1)(vii))

A. *Rejection of claims 46-48 under 35 U.S.C. §103(a)*

Claims 46-48 have been rejected under 35 U.S.C. §103(a) for being obvious over Roberts (WO 94/22476) in view of Lund (U.S. Patent 3,920,811). Appellants request reversal of this rejection.

The method recited in claims 46-48 is distinguished by providing immunization using 2 ml of a multicomponent clostridial vaccine comprising Moraxella Bovis and an encapsulating polymer adjuvant. Contrary to the teaching of the cited prior art, the claimed method reduces injection site lesions by at least 41% compared with a conventional 5 ml vaccine composition. These results are in contrast to the objective of the Roberts publication, which is directed to reducing injection site lesions by avoiding the encapsulating polymer adjuvants required in Appellants' claims.

Roberts' invention is the preparation of clostridial vaccines "made without stabilizing carriers or depot adjuvants, but rather with a readily dispersible, water-soluble adjuvant, saponin." (Page 1, paragraph 1).

Lund is relied on for teaching adjuvant polymers that are retained at the site for prolonged slow release wherein the active agent is absorbed into the polymer; that is, depot adjuvants.

Although mentioning all known varieties of adjuvants, Roberts specifically teaches that multicomponent clostridial vaccines should be made up using readily dispersible, water-soluble adjuvants rather than depot adjuvants, including CARBOPOL ™, because those adjuvants "...usually provoke severe persistent local reactions, such as granulomas, abscesses and scarring..."which are reported to be "responsible for carcass blemish which requires expensive trimming, a consideration when the vaccine has been injected into muscle tissue destined to be a valuable cut of meat." (Page 2, lines 24-33). Thus, Roberts teaches against using polymeric adjuvants. Furthermore, the dosage ranges disclosed apply specifically to "vaccines of the present invention," the vaccines with soluble adjuvants. (Page 8, lines 24-33).

The Examiner improperly, therefore, combines the teaching found in Roberts with Lund, which, as the Examiner states, "teaches an adjuvant polymer, such as CARBOPOL™, [which]

is retained at the site for prolonged slow release that acts by absorbing the active agent onto the polymer." (Lund, columns 1-2, lines 67-5).

Appellants submit that no prima facia case of obviousness has been made. "[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them [to achieve a desired result] is more likely to be nonobvious." KSR International v. Teleflex Inc. et al., 127 S.Ct. 1727 at 1740 (2007); United States v. Adams, 383 U.S. 39 at 51-52, 86 S.Ct. 708 (1966).

One of ordinary skill in the art reading Roberts would never find reason to combine it with Lund as Roberts teaches against using the depot adjuvants of Lund. " A reference may be said to be teaching away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the Applicant." Ormco Corporation v. Align Technology, Inc., 463 F.3d 1299 at 1308, C.A. Fed. (Cal.), 2006; In re Kahn, 441 F.3d at 990 (Fed.Cir. 2006).

That is, Roberts teaches that low tissue reactivity is accomplished using dispersible, soluble adjuvants. "The present invention is based on the surprising discovery that the water soluble adjuvant, saponin, can be used in place of a depot adjuvant in multicomponent clostridial vaccines for cattle." (Page 2, lines 22-24).

On page 1, the first full paragraph, Roberts states:

> "The present invention relates generally to vaccine compositions and methods of using the same. More specifically, the invention pertains to multicomponent clostridial vaccines **made without** (emphasis added) stabilizing carriers or **depot adjuvants** (emphasis added), but rather with a readily dispersible, water-soluble adjuvant, saponin." (Page 1, lines 12-15).

Roberts teaches against using encapsulating adjuvants, such as those used in Appellants' invention and those to which Lund is directed. On page 2, the paragraph beginning on line one, Roberts recites:

> "Other potent **depot adjuvants** (emphasis added), such as water-in-oil emulsions and carbopol, have also been used in clostridial vaccines. The above-described adjuvants, although increasing antigenicity, **usually provoke severe persistent local reactions** (emphasis added), such as granulomas, abscesses and scarring, when injected subcutaneously or intramuscularly. These local reactions are, in turn, responsible for carcass blemish which requires expensive trimming, a consideration when the vaccine has been injected into muscle tissue destined to be a valuable cut of meat." (Page 2, lines 1-7).

On page 4, in the paragraph beginning on line 24, Roberts states:

> "**Central to the present invention is the surprising discovery** (emphasis added) that stable, potent, multicomponent clostridial vaccines can be made **without the use of depot adjuvants** (emphasis added). In particular, the present invention provides for vaccines including rapidly dispersed, soluble adjuvants, that is, **adjuvants that are not retained at the injection site for a significant period of time, thereby exhibiting low tissue reactivity** (emphasis added). The vaccines can be administered intramuscularly and subcutaneously without the harmful side effects and chronic inflammatory responses that produce granulomas and abscesses, seen with other clostridial vaccine compositions when administered via these routes." (Page 4, lines 24-32).

Roberts clearly teaches against using an encapsulating polymer adjuvant that releases antigens slowly at the site of injection. Any skilled practitioner reading Roberts must conclude that using such polymer adjuvants would result in high incidents of "severe persistent local reactions, such as granulomas, abscesses and scarring," that would in turn be "responsible for carcass blemish which requires expensive trimming." Appellants' invention requires the use of such encapsulating polymer adjuvants and yet achieves the minimization of injection site lesion formation (a reduction of at least 41%) by administering 2 ml doses rather than conventional 5 ml doses. Unexpectedly, in view of the prior art, Appellants

achieved protective immunity using a depot adjuvant in a 2 ml dose while reducing injection site lesion formation.

The ordinary practitioner would never, based on the teaching of Roberts, exchange the adjuvant of Roberts for an equivalent encapsulating polymer, as taught by Lund, as Roberts clearly teaches that such polymer adjuvants result in deleterious injection site lesion formation. Roberts does not suggest in any way that these problems could be overcome with low dose encapsulating polymer formulations.

The ordinary practitioner would never combine the teachings of Roberts and substitute an encapsulating polymer in view of Lund. Following the teaching of Lund, which is the use of a prolonged release polymer adjuvant, it would be expected, based on Roberts, to "provoke severe persistent local reactions, such as granulomas, abscesses and scarring,..." that "are, in turn, responsible for carcass blemish...." (Roberts, Page 2, first paragraph). The ordinary practitioner reading Roberts would never adopt the use of the adjuvant polymers taught by Lund at any dosage.

The Supreme Court stated in KSR (*KSR International Co. v. Telefax Inc.*, 127 S. Ct.1727 (2007)) that Graham factors still control the obviousness inquiry. Those factors are: 1) "the scope and content of the prior art;" 2) "differences between the prior art and the claims;" 3) "the level of ordinary skill in the pertinent art;" and 4) "objective evidence of non-obviousness". *KSR, 127, S. Ct. at 1734* (quoting *Graham v. John Deere Co. of Kansas City*, 86 S. Ct. 684 (1966)). Addressing these factors, the scope and content of the prior art include separate and opposing teachings by Roberts and Lund, one directing the ordinary practitioner to soluble adjuvants and the other directing the practitioner to depot adjuvants. The differences between the prior art and the claims include Roberts' teaching that soluble adjuvants are required to reduce injection site lesion formation contrasted with Appellants' discovery that depot adjuvants can be used while still reducing injection site lesion formation, and thus the reduction of spoilage. The level of ordinary skill in the art is relatively high, more than sufficient for the ordinary practitioner to conclude, reading Roberts, that depot adjuvants would result in injection site lesions. Again, contrary to Roberts, the objective evidence of non-obviousness is Appellants' use of depot adjuvants, encapsulating polymer adjuvants,

which result in the slow release of antigen at the site of injection, but, at the same time, accomplishing the reduction of injection site lesion formation.

The primary reference teaches against using encapsulating polymer adjuvants and the secondary reference, in addition to being inconsistent with the primary reference, does not address the issue of injection site lesions and does not suggest using low dose immunization methods..

Appellants respectfully submit that the prior art references have been improperly combined as they reveal to the skilled practitioner two opposing teachings for selecting adjuvants and, further, relying on a primary reference that teaches against Appellants' use of encapsulating polymer adjuvants and the use of the adjuvants of the secondary reference.

If it can be concluded that Roberts teaches vaccine administration in 2ml dosages, which Appellants do not concede, the dosages taught apply only to vaccines based on soluble adjuvants and not vaccines comprising depot adjuvants, such as Appellants' encapsulating polymer adjuvants.

On page 8 of Roberts, the formulation of the "dispersible, non-depot adjuvant" composition is described and, although dosages are merely mentioned in passing, giving broad ranges, the dosage ranges mentioned specifically refer to "vaccine compositions of the present invention." (Page 8, lines 24-25). "For example, to immunize cattle with the clostridial vaccine compositions described above, [dispersible, non-depot adjuvant compositions] generally between 0.5 ml to 10 ml will be administered, more preferably 1 to 5 ml." (page 8, lines 30-32). No mention is made for dosage ranges to be used with non-dispersible adjuvants, or any other types of adjuvants. Furthermore, beyond the broad ranges mentioned, all specific examples provided by Roberts of such saponin, soluble adjuvant vaccine compositions were administered to cattle using 5 ml dosages (Example 3, pages 13-18).

B. ***Rejection of claims 46-48 under 35 U.S.C. §112, first paragprah)***

Claims 46-48 have been rejected under 35 U.S.C. § 112, first paragraph, for not complying with the written description requirement. The Examiner objected that Appellants did not point to the support in the specification showing that injection site lesion formation

was reduced at least 40% compared with an injection of 5 ml of the same vaccine. The Examiner did not accept Appellants' direction to page 54, Tables 12 and 13, for support, alleging that after weaning the reduction was only 33.2%.

Appellants submit that the written description requirement has been met and this rejection should be withdrawn. In Table 12 on page 54, the reduction in the number of lesions from the 5 ml dose when using the 2 ml dose is from 79.5% of the cattle to 46.3% of the cattle, a reduction of 41% in the number of cattle having lesions. The specific types of lesions are reported in Table 13. Appellants believe that these results support a limitation as presently set forth in the claims that injection site lesion formation is reduced at least 41% compared with an injection of 5 ml of the vaccine. The "at least" term finds support in Table 14 on page 55, wherein the incident of lesions is reduced from 69.4% to 30.3%, an overall reduction of 56.3%. The dramatic reduction in lesion formation illustrates an unexpected result achieved following Appellants' claimed method, further demonstrating nonobviousness..

VIII. DESCRIPTION OF CLAIMS APPENDIX (37 C.F.R. §41.37(c)(1)(viii))

An appendix containing a copy of all the claims involved in the appeal is provided on pages 19.

IX. DESCRIPTION OF EVIDENCE APPENDIX (37 C.F.R. 41.37©(1)(ix))

None.

X. DESCRIPTION OF RELATED PROCEEDINGS APPENDIX (37 C.F.R. §41.37(c)(1)(x))

None.

XI. Fee payment and extension request

Appellant authorizes the Commissioner to charge Deposit Account No. **02-2334** for the $510.00 fee under 37 CFR §41.20(b)(2) for filing this appeal. Appellant also requests a one-month extension to file this brief, and authorizes the Commissioner to charge Deposit Account No. **02-2334** for the corresponding extension fee under 37 CFR §1.17(a)(5). Appellant does not believe that any other fee is due in connection with this filing. If, however, Appellant does owe any such fee(s), the Commissioner is hereby authorized to charge the fee(s) to Deposit Account No. **02-2334**. In addition, if there is ever any other fee deficiency or overpayment in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **02-2334**.

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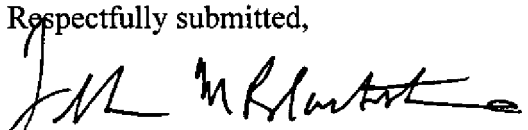
Appellants submit that the pending claims are in condition for allowance, and requests the rejections in the December 20, 2007, final Office action be reversed, and claims 46-48 be allowed.

Respectfully submitted,



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APPENDIX A
Claims Appendix (37 C.F.R. §41.37(c)(1)(viii))

46. A method of immunizing cattle without significant injection site lesion formation, comprising injecting into said cattle about 2 ml of a multicomponent vaccine for cattle comprising an immunogenically effective combination of a protective antigen component from six clostridial organisms, a protective antigen component from at least one non-clostridial organism, which is Moraxella Bovis (M.Bovis), and an encapsulating polymer adjuvant, whereby the encapsulating polymer adjuvant releases antigens slowly at the site of injection and whereby injection site lesion formation is reduced at least 41% compared with an injection of 5 ml of said vaccine into said cattle and effective immunization is accomplished.

47. A method of immunizing cattle without significant injection site lesion formation, comprising injecting into said cattle about 2 ml of a multicomponent vaccine for cattle comprising an immunogenically effective combination of protective antigen components from seven clostridial organisms, a protective antigen component from at least one non-clostridial organism, which is M. Bovis, and an encapsulating polymer adjuvant, whereby the encapsulating polymer adjuvant releases antigens slowly at the site of injection and whereby injection site lesion formation is reduced at least 41% compared with an injection of 5 ml of said vaccine into said cattle and effective immunization is accomplished.

48. A method of immunizing cattle without significant injection site lesion formation, comprising injecting into said cattle about 2 ml of a multicomponent vaccine for cattle comprising an immunogenically effective combination of the protective antigen components *Cl. chauvoei, Cl. septicum, Cl novyi, Cl. perfringens* type C, *Cl. perfringens* type D, *Cl. sordellii*, *Cl. tetani* and *Cl. haemolyticum*, a protective antigen component from at least one non-clostridial organism, which is M. bovis, and an encapsulating polymer adjuvant, whereby the encapsulating polymer adjuvant releases antigens slowly at the site of injection and whereby injection site lesion formation is reduced at least 41% compared with an injection of 5 ml of said vaccine into said cattle and effective immunization is accomplished.

APPENDIX B

Evidence Appendix (37 C.F.R. §41.37(c)(1)(ix))

None.

APPENDIX C
Related Proceedings Appendix (37 C.F.R. §41.37(c)(1)(x))

None.